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EXAMINER
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ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
07/26/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/779,746	GREER, SHELDON B.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-75* is/are pending in the application.

4a) Of the above claim(s) *60-66 and 71-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/15/2009 has been entered.

Suspension of Action

Applicant filed a Letter Requesting Suspension of Action on 9/30/2009. Applicant requested that the Office suspend action on the application for a period of six months in order for Applicant to obtain data in a Phase I trial.

The period of suspension of action expired on 3/30/2010. No additional data or submissions have been received from Applicant.

Formal Matters

Applicants' response and amendments to the claims, filed 7/15/2009 and 9/15/2009, are acknowledged and entered. Claims 60-66 and 71-75 remain withdrawn from consideration. Claims 67-70 are pending and under examination.

Response to Arguments

Applicants' arguments, filed 7/15/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 102 – New Ground of Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 67 and 69-70 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Greer** (WO 85/01871; Published May 9, 1985).

Claimed Subject Matters

Instant claims 67 and 69-70 recite methods of "achieving tumor control in at least one human tumor in a patient" consisting of administering CldC and tetrahydrouridine and thereafter radiation. The Examiner is interpreting the claims to encompass administering to a patient CldC and tetrahydrouridine (H_4U) in amounts effective to produce elevated levels of CldUMP and CldU and the tumor is then exposed to a dose of radiation.

Teachings of Greer

Greer teaches a method of sensitizing neoplastic tissue to radiation comprising the administration of 5-chlorodeoxycytidine (5-CldC) co-administered with tetrahydrouridine (H_4U) (Abstract; page 3, lines 4-14). Further, Greer teaches that when CldC is administered with H_4U, CldC should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 16-28). The reference thus explicitly teaches administration of CldC and tetrahydrouridine to a patient with a tumor followed by exposing the tumor to radiation. Also see Table 1 at page 41 of Greer, wherein on days WED and THURS, CldC and H_4U are administered prior to radiation.

The invention of Greer provides therapeutic materials and procedures for treating solid tumors using X-ray or gamma ray, beta, neutron and other radiation sources (page 2, lines 10-15). According to one aspect of the invention, patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2'-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is **preferably administered** with a

deamination inhibitor, preferably tetrahydrouridine, for a period of time until amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14). The reference thus explicitly teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine to a patient having a tumor about to undergo radiation therapy.

Low concentrations of tetrahydrouridine are taught to protect the nucleoside analogs from systematic catabolism whereas with high concentrations of tetrahydrouridine, CldC "should be converted preferentially at the tumor site to CldUMP in human tumors possessing high levels of deoxycytidine kinase and dCMP deaminase (page 9, lines 20-28). Claims 1-4 of the WO document explicitly recite methods of sensitizing "susceptible neoplastic tissue" to radiation by administering the instantly claimed compounds.

Although pretreatment with an inhibitor of pyrimidine biosynthesis (*e.g.*, the agents excluded from the methods instantly claimed) is also disclosed in the reference, such inhibitors are not required, and it is clear that Greer unequivocally teaches administering a combination of 5-chloro-2'-deoxycytidine and tetrahydrouridine so as to sensitize tumors to radiation therapy (page 3, lines 4-14). While such therapy may be *enhanced* by co-administration with an inhibitor of pyrimidine biosynthesis, the fact remains that 5-chloro-2'-deoxycytidine and tetrahydrouridine are alone effective to sensitize tumors to radiation when administered without such an inhibitor of pyrimidine biosynthesis.

The instantly claimed methods only require that a tumor be sensitized to radiation when a patient is administered 5-chloro-2'-deoxycytidine and tetrahydrouridine followed by an effective level of radiation. Table 1 of Greer (page 41) explicitly teaches administering to a patient CldC + H4U followed by radiation wherein none of PALA, FdC, 4-N-methyl FdC, and FdU are administered to the patient (days WED and THURS of the "Standard Protocol" in Table 1).

It is clear from the Greer reference that administration of 5-chloro-2'-deoxycytidine and tetrahydrouridine is effective to sensitize tumors to irradiation. As such, Greer clearly anticipates the claimed method of treating tumors comprising sensitizing tumors to radiation by administering 5-chloro-2'-deoxycytidine and tetrahydrouridine and exposing a patient to an effective level of radiation.

With regard to the amounts of CldC and/or tetrahydrouridine as recited in the instant claims, Greer teaches dosages of these agents at page 18, Table II. In the absence of evidence to

the contrary, such doses of CldC are "sufficient to produce elevated levels of CldUMP and CldU" and the doses of tetrahydrouridine are effective to "prevent toxicity of the CldC" as recited in the instant claims.

Response to Arguments

Applicant's arguments have been fully and carefully considered but are not deemed persuasive. Applicant argues that assuming arguendo that Greer discloses co-administering CldC and tetrahydrouridine, it does not disclose the amount of tetrahydrouridine that is required by the present claims.

This argument is not persuasive because Applicant has provided no factual evidence that the doses of tetrahydrouridine disclosed in Greer at page 18, Table II are not effective to prevent toxicity of CldC as recited in the instant claims. In fact, Greer explicitly teaches at page 4, lines 7-18:

> "Rapid catabolism and **generalized toxicity** have limited the use of 5-halogenated analogs of deoxyuridine as tumor sensitizers. In one approach to this problem, 5-halogenated analogs of deoxycytidine (dC) or of 2'-halo 2'-dexocytidine were utilized, which are not catabolized unless they are deaminated. **To prevent deamination by cytidine deaminase (CD)**, which is extremely active in human serum, **it is preferred, according to the invention, to administer tetrahydrouridine (H4U), a potent inhibitor of this enzyme, either concurrently with, or at about the same time as, administration of the deoxycytidine compound**." (emphasis added)

Accordingly, the Examiner is not persuaded by Applicant's argument that Greer does not teach administration of tetrahydrouridine in a dose effective to prevent toxicity of the CldC.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Greer** (WO 85/01871; Published May 9, 1985) as applied to claims 67 and 69-70, *supra*.

Claimed Invention

Instant claim 68 recites that the tumor is exposed to a dose of radiation of 23.3 to 70 Gy.

Teachings of Greer

Greer teaches as applied to claims 67 and 69-70 *supra*. Greer further teaches that the radiation dose will be either the same or ¼ or ¾ the dose given to patients not receiving the pretreatment sensitization schedule (page 17, lines 16-24). Greer further teaches that the course of treatment can be repeated until the patient receives a total dose of 3000 to 7000 rads, which is equivalent to 30 to 70 Gy (100 rad = 1 Gy) (page 18, lines 2-10).

Findings of Fact (FF)

I) Greer teaches combined administration of CldC and tetrahydrouridine to sensitize tumors to radiation; and

II) Greer teaches exposing patients to a total dose of 3000 to 7000 rads (*i.e.*, 30 to 70 Gy) radiation over the course of treatment.

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Analysis & Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's invention to have exposed tumors sensitized to radiation with CldC and tetrahydrouridine a dose of radiation in the range of 23.3 to 70 Gy.

The prior art recognizes that CldC sensitizes tumors to radiation and that tetrahydrouridine can prevent toxicity associated with CldC administration. Specifically, Greer teaches that patients having tumors requiring radiation therapy are administered, preferably on a slow release basis, 5-chloro-2'-deoxycytidine and/or 5-chloro 2'-halo-2'-deoxycytidine. The deoxycytidine compound is **preferably administered** with a deamination inhibitor, preferably tetrahydrouridine, for a period of time until amounts sufficient to sensitize tumor tissue to radiation are present in the tumor tissue (page 3, lines 4-14); that the radiation dose will be either the same or ¼ or ¾ the dose given to patients not receiving the pretreatment sensitization schedule (page 17, lines 16-24); and that the course of treatment can be repeated until the patient receives a total dose of 3000 to 7000 rads, which is equivalent to 30 to 70 Gy (page 18, lines 2-10).

Thus, Greer teaches, suggests and motivates coadministration of CldC and tetrahydrouridine to patients with tumors so as to sensitize the tumors to radiation therapy. As such, the skilled artisan would have been motivated to adjust the radiation dose administered to such patients in order to elicit the most effective therapy.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 67-70 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3-5 of U.S. Patent No. 4,894,364. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the '364 patent encompass the administration of CldC and tetrahydrouridine to sensitize tumors to radiation.

Response to Arguments

Applicant's arguments have been fully and carefully considered by they are not deemed persuasive. Applicant argues that the claims have been amended to include the transitional phrase "consisting of" and thus this rejection has been obviated and should be withdrawn.

Applicant's arguments are not convincing. Claim 1 of the '364 patent recites a method of sensitizing susceptible tumor tissue to x-ray, gamma, beta, UV, or near visible light radiation, which method comprises administering to a patient a radiation-sensitizing amount of a deoxycytidine compound (*e.g.*, CldC) and a systemic deamination preventing amount of a deamination inhibitor selected from the group containing tetrahydrouridine and 2'-deoxytetrahydrouridine. As claim 1 does not recite or require administration of any other active agents, it obviates the instantly recited "consisting of" language. It would have been obvious to subsequently expose sensitized tumors to radiation as recited in the instant claims because the method of the '364 patent is a method of "sensitizing susceptible tumor tissue to x-ray, gamma, beta, UV, or near visible light radiation".

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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